REMARKS

Claims 1, 3, 4, 6 – 16, and 22 – 28 are pending. Claims 1, 3, 4, and 6 – 16 are under consideration, and claims 22 – 28 are withdrawn.

Reconsideration and allowance of the application are respectfully requested.

Requirement for Restriction

Applicant thanks the Examiner for vacating the requirement for an election of species as set forth in the Restriction Requirement mailed June 28, 2005.

Priority

Applicant also thanks the Examiner for acknowledgment of the papers filed under 35 U.S.C. § 119(a)-(d).

Claim Rejections – 35 U.S.C. § 103(a)

The Office Action rejects claims 1, 3, 4, and 6 – 16 under 35 U.S.C. 103(a) as allegedly being unpatentable over Tanaka et al. (WO 97/02832; hereinafter TANAKA), in view of Yamahira et al. (U.S. Patent No. 4,244,943; hereinafter YAMAHIRA). In particular, the Office Action states that TANAKA teaches a lyophilized composition comprising hepatocyte growth factor, a stabilizer, sodium chloride, buffer, and a surface active agent. The Office further states that while TANAKA teaches that the stabilizing agent can include amino acids in general, TANAKA does not explicitly teach inclusion of arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid as the stabilizing agent.

For this missing feature the Office relies upon YAMAHIRA, which teaches the lyophilization of urokinase using a combination of HSA with a polar amino acid such as arginine, aspartic acid, etc. The Office further alleges that it would have been obvious to one of ordinary skill in the art to modify the invention of TANAKA by selecting any of the polar amino acids taught by YAMAHIRA as stabilizing agents. The Office further alleges that "[t]he motivation to do so would be to choose an amino acid known to be effective in stabilizing lyophilized preparations" (see Office Action dated September 19, 2008 at page 5, lines 3 – 5).

Finally, with regard to the preparation of the claimed composition from an aqueous solution containing the hepatocyte growth factor at a concentration of lower than 5 mg/mL, the Office notes that while TANAKA does not explicitly teach such a limitation, it has not been given patentable weight in the absence of evidence that the claim element distinguishes the claimed product over that rendered obvious by the prior art. The Examiner additionally notes that the claimed concentration of the solution could easily be optimized by varying the amount of solvent and that it is within the skill of the artisan to do so (see Office Action at page 6, lines 2 – 12).

In response, Applicant respectfully submits that the claimed invention is not unpatentable over TANAKA in view of YAMAHIRA. In particular, Applicant submits that the Office has failed to establish a *prima facie* case of obviousness, at least because the Office has failed to show that the cited art, either alone or in combination would yield the invention as claimed. Specifically, neither TANAKA nor YAMAHIRA, either alone or in combination, teach "[a] lyophilized preparation comprising a hepatocyte growth factor, a stabilizing agent comprising arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid, or a pharmacologically acceptable salt thereof, for preventing formation of an aggregate of the hepatocyte growth factor, sodium chloride, and a

buffering agent, which is prepared from an aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/mL."

As the Office concedes, TANAKA does not explicitly teach the use of an amino acid other than glycine or alanine as a stabilizer. Applicant further submits that TANAKA also published as Japanese Patent Unexamined Publication No. 9-25241, which has been described in the instant specification. In particular, the instant specification makes clear that the present invention represents an improvement over the HGF composition taught in TANAKA, at least insofar as (1) TANAKA's lyophilized preparation of HGF was prepared at a high concentration, (2) TANAKA's use of citric acid as a buffering agent meant the re-dissolved preparation was acidic, and (3) the resulting solution taught by TANAKA had a high osmotic pressure, which causes problems of pain at administration by injection, or inflammatory rejection and hemolysis at the site of administration (see specification at page 2, second full paragraph).

Furthermore, as described in Test Example 4 and Table 8 on pages 23 – 25 of the instant specification, when compositions such as those taught by TANAKA comprising glycine or alanine as stabilizers were prepared in compositions wherein HGF concentration was low, i.e., lower than 5 mg/mL HGF, it was found that aggregate formation was accelerated and storage stability was lowered (see also, e.g., Examples 5 and 6 at page 12 of the specification). From these comparative experimental results it can be understood that a lower concentration of HGF gave aggregation of HGF and reduced stability when glycine (Example 5) or alanine (Example 6) were used as a stabilizer.

Moreover, Applicant submits that the Office has failed to establish a *prima facie* case of obviousness, at least because a person of ordinary skill in the art would not combine the art as

asserted by the Office. TANAKA teaches a lyophilized composition comprising HGF, a stabilizer, sodium chloride, a buffer and/or a surface active agent. The stabilizer can be an amino acid such as glycine or alanine. YAMAHIRA states that "a combination of HSA with a polar amino acid has *a specific stabilizing effect on urokinase*" (see Col. 1, line 26 – 30, emphasis added). Thus, YAMAHIRA does not disclose the use of arginine or any other polar amino acid as a broadly applicable stabilizing agent with respect to any lyophilized protein. In fact, YAMAHIRA fails to disclose the use of the polar amino acids with any protein other than urokinase, and the Office has failed to provide such a connection between urokinase and HGF. Applicant further submits that urokinase is a totally different protein than HGF: urokinase is a serine protease, whereas HGF is a growth factor that accelerates proliferation and growth of hepatocytes.

Based at least on the foregoing, Applicant submits that the claimed invention is not fairly suggested or anticipated by TANAKA and/or YAMAHIRA, either alone or in combination. Accordingly, Applicant respectfully requests reconsideration of the rejection under 35 U.S.C. § 103(a) and withdrawal of the same.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the objections and rejections of record, and allow each of the pending claims. Applicant therefore respectfully requests that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

The Office is authorized to charge any required fee to Deposit Account No. 19-0089.

Should the Examiner have any questions regarding this Response, the this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
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